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nerve palsy or paralysis of one or more extremities. Diagnosis should be confirmed by spinal fluid examination, and a neurologist should be consulted for diagnostic assistance.

e. Asymptomatic neurosyphilis is manifested only by an abnormal spinal fluid.

f. Ocular relapse may be manifested by iritis, usually unilateral, or optic neuritis, or neuroretinitis, which may be unilateral or bilateral. An ophthalmologist should be consulted.

g. Osseous relapse is manifested by severe pain, often nocturnal, in the long bones, most often the tibiae, or severe headaches when cranial bones are affected. Local tenderness is often very acute.

h. To date, no instance of true treatment resistance to penicillin insofar as failure of mucocutaneous lesions to heal or treponemas to disappear, has been observed.

9. Management of Penicillin Failures.

a. Cases of neurologic relapse and asymptomatic neurosyphilis will receive a total of 4,000,000 Oxford units of penicillin while in hospital, and then be managed in accordance with the directions contained in Circular Letter No. 103, "Management of Neurosyphilis", Office of the Chief Surgeon, 9 August 1944. The penicillin will be administered in 80 consecutive injections of 50,000 units each at 3-hour intervals day and night for 10 days. In patients in whom the possibility of a severe Herxheimer reaction may be considered to have serious potentialities, the initial doses of penicillin may be reduced to 10,000 units, but it should be possible to reach the full dosage schedule within 48 hours. Patients with Grade I and II spinal fluids will be continued on standard mapharsen-bismuth therapy after completion of the penicillin course.

b. Patients with other types of treatment failure will receive a second course of treatment consisting of concurrent administration of penicillin and Mapharsen, as follows:

Penicillin: 80 injections of 50,000 units each given intramuscularly at 3 hour-intervals day and night for ten days, a total of 4,000,000 units.

Mapharsen: 60 mgms. intravenously daily for 8 days, a total of 480 mgms.

(1) Management of reactions to Mapharsen. Certain patients will prove more or less intolerant to Mapharsen given in accordance with the above schedule. However, unless the patient has previously received Mapharsen, it is not likely that such reactions will develop prior to the 5th day of treatment. The reactions to be looked for are:

(a) Fever. Severe reactions to intensive arsenotherapy of this type almost never occur in the absence of accompanying or preceding fever. In any patient showing a rise in temperature above 100°F, the patient should be carefully examined clinically, especially for the reactions listed below, and adequate laboratory studies performed.

(b) Toxic encephalopathy.

(c) Neutropenia.

(d) Toxicodermal reactions of various types, usually a morbilliform or scarlatiniform eruption accompanied by fever.

(e) Hepatitis.

(2) A reaction to Mapharsen of more than slight severity is an indication for discontinuance of such medication. The penicillin course will be continued to completion, and the patient then placed on observation.

(3) Patients with severe reactions to Mapharsen should be treated with injections of BAL, four injections of 2 c.c. each during the first 24 hours, and 2 c.c. daily for the next four days.

10. Management of patients already on standard Mapharsen-bismuth treatment for syphilis who receive penicillin for a surgical wound or an intercurrent medical infection.

Insofar as is possible without prejudice to the general medical and surgical treatment of such patients, penicillin therapy to a total of 2,400,000 units should be given while the patient is in hospital. The patient will then be placed on observation as far as his syphilitic infection is concerned. It is impossible at present to evaluate the influence of partial courses of penicillin in the cure of syphilis, and it is important, therefore, that the full course of penicillin be given before the patient is placed on observation.

THE TREATMENT OF GONORRHOEA WITH PENICILLIN*

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Although penicillin has been used in the treatment of gonorrhoea for a short time only, it has already established itself as the most valuable remedy for this disease that has yet been discovered. The short life history of the gonococcus and the relative accuracy of tests for cure have made the assessment of the value of penicillin more simple and accurate in gonorrhoea than in syphilis.

Penicillin became available to the medical services of the Armed Forces in 1944 at a most opportune time, and its use then in cases of sulphonamide-

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resistant gonorrhoea at home and abroad, and in acute gonorrhoea in the men of the invasion armies, must have saved an enormous amount of man-power.

Method of administration and test of cure

My own experience with penicillin is limited to the use of the sodium salt administered intramuscularly in aqueous solution. Putnam, Welch and Olansky have shown that the various salts of penicillin are all equally effective in the treatment of sulphonamide-resistant gonorrhoea.

My patients were almost all treated in hospital until clinical evidence of disease had disappeared. Progress was studied by microscopical examination of specimens of urethral secretions taken each morning before urination. After completion of hospital treatment most patients returned once weekly for 3 consecutive weeks for inspection, again at the end of 3 months for a test of cure, and at the end of 6 months for a final serological test for syphilis. Prostatic massage or

TABLE 1—TREATMENT OF ACUTE GONORRHOEA IN MALES WITH PENICILLIN IN DIVIDED DOSES

DOSEAGE	RESULTS OF TREATMENT	Number of cases	Percentage
100,000 units of penicillin in 5 doses of 20,000 units at 3-hourly intervals	Cured	220	84
	Requiring adjuvant treatment for residual non-gonococcal urethritis	31	12
	Early relapse (within 14 days)	6	2
	Late relapse (14 days and over)	5	2
	Total ...	262	

Early relapses included one case of epididymitis. Late relapses occurred, one at 2 weeks, one at 4 weeks, and 3 at 3 weeks after treatment. All were subsequently cured by repetition of penicillin treatment.

instrumentation was not usually performed before the test of cure, because I am opposed to unnecessary and traumatizing examinations. The test of cure included examination of the prostate and vesicles and their secretions, the passage of a steel sound, sometimes urethroscopy, and a serological test for syphilis. Control by means of culture examination was unfortunately impossible, and this omission may have made our estimated cure rate err on the high side. (Comparison may be made with the work of Lapenta, Weckstein and Sarnoff.)

Acute gonorrhoea

Almost from the beginning, most of the patients whom I have treated for acute gonorrhoea have received a total of 100,000 units of penicillin, in 20,000-unit doses, at three-hourly intervals. This spacing was used originally so that the treatment scheme would fit in with the arrangements made for treating syphilis. The results were good, so that, apart from the experimental series, routine treatment has continued on the same plan. Table 1 gives details of 262 men who have been treated up to 3 months ago, each with 100,000 units of penicillin.

Although penicillin caused the disappearance of gonococci from the secretions in 96 per cent of cases in this series, no less than 12 per cent of the total number of patients required adjuvant treatment in the form of irrigations, a course of sulphonamide, or both.

In all cases gonococci had disappeared from the urethral discharge by the end of 24 hours. The average time for disappearance of signs and symptoms of urethritis in the 84 per cent of cured cases was 4 days. Evidence of failure of treatment, as shown by the reappearance of gonococci in the urethral secretions, was present in some cases within a few days, but in others relapses occurred only after several weeks. All the patients who had relapses were subsequently cured with further penicillin treatment at the same dosage level.

Other dosage and dose-spacing schemes have been tried. In one series of 50 cases a dose of 100,000 units of penicillin was given in a single injection. This

was effective in removing gonococci from the urethral discharge within 4 hours. Relapses were frequent, and at first such patients were treated with another single injection of 100,000 units. Repeated failures led to the use of the multiple dose method in such cases. Although gonococci had disappeared in every case within 4 hours, early relapses occurred in 30 cases: in 16 cases after 2 days, in 7 cases after 3 days, in 4 cases after 4 days and in 3 cases after 5 days. Late relapse, between 16 and 40 days, was noted in 5 cases. Reinfection, which occurred in 2 cases, responded to treatment with 5 injections each of 20,000 units. The results are shown in Table 2.

In another series 20 cases were treated with two injections each of 50,000 units of penicillin at 8 hours' interval. Two relapses occurred, one at 6 and the other at 8 days after treatment, and the patients were cured subsequently with a total of 200,000 units of penicillin in 5 doses at three-hourly intervals.

My earliest cases were treated with 100,000 units of penicillin given in one dose of 50,000 units and 2 of 25,000 units at four-hourly intervals. The results were comparable with those obtained from the 5 doses of 20,000 units. I have also used penicillin in doses of 50,000 and 60,000 units divided in various ways, but this line of investigation was soon discarded as the results were uniformly bad. In the last two months, in order to see whether or not the number of cases requiring adjuvant treatment could be reduced, the dosage has been increased to 200,000 units given in 5 doses of 40,000 units at three-hourly intervals. So far 143 cases have been treated. Early relapses have occurred in 2 cases, and the percentage of cases requiring adjuvant treatment has been 20 (29 cases).

Combined penicillin and sulphonamide treatment

Oard and others have published the results of a trial of combined penicillin and sulphonamide treatment for acute gonorrhoea. The treatment consisted of the oral administration of 8 grammes of sulphathiazole in divided doses on the first day, and of 4 grammes of sulphathiazole on the second day, when 50,000 units of penicillin were injected at the rate of 10,000 units every 3 hours. Among 232 cases thus treated, there were 10 failures—4·3 per cent. The failure rate in white men was 8·6 per cent. and in negroes only 2·5 per cent. The failures were all promptly cured by treatment with 100,000 units of penicillin. The failure rate with 50,000 units of penicillin alone is stated to be between 10 and 20 per cent, and Oard and his colleagues conclude that sulphathiazole and penicillin appear

TABLE 2—TREATMENT OF ACUTE GONORRHOEA IN MALES WITH PENICILLIN IN A SINGLE DOSE

DOSAGE	RESULTS OF TREATMENT	Number of cases	Percentage
100,000 units of penicillin in a single dose	Cured (no adjuvant treatment required)	15	36
	Cured (adjuvant treatment required)	3	
	Not cured (failed once with single dose)	25	64
	Not cured (failed twice with single dose)	1	
	Not cured (failed three times with single dose)	1	
	Not cured (relapsed 16-40 days after treatment)	5	
	Total	50	

All the infections which failed to respond to a single injection of 100,000 units were subsequently cured, with one exception, by 5 injections of 20,000 units at 3-hourly intervals. The one exception was treated successfully with a second injection of 100,000 units.

to have a mutually enhancing effect against the gonococcus.

Lees, however, was not impressed by the results in a small series of cases treated with 5 grammes of sulphathiazole daily for 6 days and with 30,000 units of penicillin on the fifth day, and did not consider the experiment to be worth pursuing.

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Prolongation of the action of penicillin

The rapidity of excretion of penicillin requires that the time of injections be closely approximated in order that effective blood levels may be maintained. In order to effect a reduction in the frequency of injections various retarding

TABLE 3—SULPHONAMIDE-RESISTANT GONORRHOEA IN MALES TREATED WITH PENICILLIN

DOSAGE	RESULTS OF TREATMENT	Number of cases	Percentage
100,000 units in 5 doses of 20,000 units at 3 hourly intervals.	Cured	101	91
	Early relapses (within 14 days)	6	5.4
	Late relapses (14 days or over)	4	3.6
	Total ...	111	

Epididymitis occurred 3 times as a relapse phenomenon. One relapsed patient was cured only after a para-urethral duct was laid open. One patient was still uncured after 3 courses of penicillin; he later received hypertherm treatment, which cured the gonorrhoea but left a residual non-gonococcal urethritis.

agents have been tried.

Romansky and Rittman report success in 11 cases out of 12 in patients with gonococcal urethritis treated with single injections of 50,000–100,000 units of penicillin contained in 2–3 millilitres of a beeswax and peanut oil mixture.

Trumper and Hutter have suggested that by continuous chilling at and round the site of intramuscular injection, bacteriostatic levels of penicillin can be maintained for a longer period, and that a saving of penicillin can be effected. They report 100 per cent cures in a series of patients with gonorrhoea treated by a single injection of 50,000 units of penicillin into chilled tissue. In a control series there was a failure rate of 45 per cent in 20 cases treated with 2 injections of 50,000 units at 6 hours' interval, and 80 per cent of failures in 10 cases treated with a single injection of 50,000 units.

Putnam, Randall and Herwick report 94 per cent of cures in a series of 68 men and women treated with a single injection of penicillin X.

Sulphonamide-resistant gonorrhoea

It seems to be the general impression that cases of sulphonamide-resistant gonorrhoea, if they present no local complications of the disease, react to adequate doses of penicillin in the same way as do fresh cases of gonorrhoea. The percentage of successful cases is roughly proportional to the dose of penicillin used.

Riba, Schmidlapp and Bosworth report 2 per cent of failures with 160,000 units, 9.8 per cent of failures with 100,000 units, and 23.6 per cent of failures with 50,000 units. Sternberg and Turner report, in a series of 1,686 cases, 98 per cent of cures with 160,000 units, 96 per cent of cures with 80–120,000 units, and 86 per cent of cures with 50,000 units. They found no difference in the results obtained by the use of individual doses of 10,000 and of 20,000 units. They state that there is no advantage in prolonging treatment beyond 12 hours. Lees, reporting on 1,897 cases, of which 93.9 per cent were cures, found that the cure rate with 100,000 units was 98 per cent, with 60,000 units 94.3, with 50,000 units 92, and with 30,000 units 80 per cent. Of 73 cases which were failures, 72 patients were cured by re-treatment with penicillin at a dosage of up to 240,000 units.

The results in the treatment of sulphonamide-resistant gonorrhoea appear to most observers to be about the same in men as in women. Duncan, Zobel and Hutcheson, however, report 8 failures in a series of 40 female cases treated with 150,000 units and conclude that women do not respond so well as do men. Their failures were all subsequently cured by one or more penicillin treatments. Cohn, Studdiford and Grunstein, reporting successful results in the treatment of sulphonamide-resistant gonorrhoea in women by the use of 75,000 units of penicillin, remark that it has no effect on *Trichomonas vaginalis* infestation.

The results in 111 male cases of sulphonamide-resistant gonorrhoea which I have treated are shown in Table 3. The results in this series are not so good as are those obtained in my series of acute gonorrhoea but, in view of the relatively small numbers, I do not consider that any conclusions can be drawn.

Treatment of failures in acute and sulphonamide-resistant infections

If treatment with penicillin fails to cause the disappearance of gonococci from the secretions, or if gonococci reappear after a day or two, a search should be

made for some local complication of gonorrhoea. If no focus of infection is found the patient should be re-treated with penicillin. The same dose as that originally used, provided that it is 100,000 units or more, is usually successful, but an increased dosage is advisable. In cases which are still uncured after a second treatment with increased dosage, I have found that a division of penicillin treatment into "courses," giving 100,000 units in divided doses on each of 2 successive days, may succeed. The rationale of this last scheme was suggested by the work of Bigger on the action of penicillin on staphylococci. So far I have found only one case of apparently uncomplicated gonorrhoea in which I was completely unable to cure the patient with penicillin, and in which gonococci persisted in spite of repeated courses of dosage up to 300,000 units.

When failure is due to a complication of gonorrhoea, re-treatment with penicillin should be delayed until local treatment has been instituted.

A persistent urethral discharge, in which no gonococci can be found, is quite common after penicillin treatment. Re-treatment with penicillin is seldom successful in curing this discharge; irrigations or sulphonamides or both are often necessary. There is no need to begin adjuvant treatment unless the urethral discharge shows no sign of stopping after 4 or 5 days.

Treatment of complications of gonorrhoea

Epididymitis.—I have treated my cases of gonorrhoea complicated by epididymitis with doses of 100,000 units, and in most cases the immediate and eventual results have been successful. In a few cases reappearance of gonococci in the secretions has necessitated re-treatment with penicillin, but there have been no late relapses. The series is too small to bear useful analysis. Penicillin has no effect upon the speed of resolution of epididymitis. Epididymitis may develop also within a day or two of the apparently successful treatment of acute and sulphonamide-resistant gonococcal urethritis. Similar findings are reported by Scarcello, and by Robinson.

Prostatitis.—I have seen 2 cases of acute prostatitis which reacted at once to penicillin treatment and 2 in which penicillin had no effect at all. In the latter cases abscesses developed and further penicillin treatment was successful after the abscesses had been opened.

Arthritis.—Opinion is divided on the results obtained from penicillin in gonococcal arthritis. Scarcello reports good results; Thompson saw no striking benefit. I have treated only a few cases with doses up to 3,000,000 units, and the results were no better than those obtained by the use of other methods. The local injection of penicillin into affected joints has been tried by Dawson and Hobby and by Thompson, but without spectacular results.

In 2 cases of Reiter's disease penicillin in doses of 200,000 and 1,000,000 units had no effect at all.

Conjunctivitis.—My personal experience is limited to one case of primary diplococcal conjunctivitis of one eye in a man who was not suffering from urethritis. The condition was markedly improved within 24 hours after treatment with 100,000 units of penicillin intramuscularly and was cured in about 4 days. Local treatment was with saline washes only. Unfortunately, there is some doubt about the bacteriological diagnosis in this case, and the organism may have been a meningococcus. Sorsby reports good results in gonococcal and other types of ophthalmia neonatorum from the local instillation of penicillin drops containing 2,500 units per cubic centimetre.

Gonococcal abscesses.—In the few cases which I have seen of localized abscesses, such as peri-urethral abscesses and abscesses of Bartholin's gland, my impression is that penicillin, in the dosage at present used, cannot supersede surgery, and that its efficacy is enhanced if its use is delayed until drainage has been established.

Salpingitis.—Greenblatt and Street, reporting on the treatment of sulphonamide-resistant gonorrhoea in women, state that the symptoms of salpingitis and pelvic peritonitis often abate within 24–48 hours after penicillin treatment. Major Bolton, at Shenley Military Hospital, also reports good results from penicillin treatment

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of salpingitis. The treatment has usually been combined with glycerin drainage of the uterus.

Vulvovaginitis in children.—This disorder appears to react well to penicillin in the dosage used for adults.

Non-gonococcal urethritis

I have used penicillin in doses of 100,000 units in the treatment of cases of urethritis in which the gonococcus could not be demonstrated as the causal agent. Some of the cases were clinically indistinguishable from gonorrhoea; others were of the type characterized by a mucoid discharge and often by a long incubation period of 10 days or more. Some were untreated; others had had previous medication with sulphonamides, lavage, and other forms of treatment. The results were uniformly bad; I therefore discontinued the original experiment after 20 cases had been treated, in order to conserve the supply of penicillin. Later experience in the treatment of obstinate cases of non-gonococcal urethritis, also of persistent non-gonococcal urethritis after penicillin treatment of gonorrhoea, has not inclined me to alter my opinion of the value of penicillin in such cases.

On the other hand, Thompson reports some improvement in a large percentage of cases in a series of 36 patients with non-specific urethritis. He also reports relief of pain in 7 out of 8 cases of non-specific epididymitis. I would recall here the opinion of Abraham, that "any treatment given about the forty-eighth hour after the onset of epididymitis is always a great success because the pain stops then whatever you do".

I suggest that it is only a slight exaggeration to say that penicillin could be used as an indicator to differentiate between gonococcal and non-gonococcal urethritis.

Complications of treatment

In my own series of cases treated for gonorrhoea there has been only one case in which there was untoward reaction to treatment. This was in a man who complained of pain at the times of injection and in whom a generalized induration of the left buttock developed 48 hours later, which lasted for two or three days before resolving without any treatment. The gonorrhoea was cured. Fever, shock, and cutaneous reactions, such as are met with after the larger doses used in the treatment of syphilis, were never encountered.

There is, as yet, no evidence of the existence of a state of penicillin-resistance comparable with the well-known sulphonamide-resistance. So far, only one of my cases has proved to be recalcitrant to penicillin treatment at all dosage levels. I have treated successfully about 20 cases of reinfections with gonorrhoea in men who had previously been treated for gonorrhoea with penicillin. It is still much too early to say whether or not penicillin-resistance, either as a host-factor or as a microbic factor, is likely to appear.

The masking of syphilis

It was suggested early that a drawback to the use of penicillin in gonorrhoea was that it might mask or render latent a coincidental syphilitic infection. In order to minimize this risk, a serological test for syphilis is required at the third and sixth month after penicillin treatment of gonorrhoea. In my opinion, with the dosage at present used, this risk is more apparent than real. I have already seen 5 cases in which men who had been treated with penicillin for gonorrhoea had developed syphilis long before the 3 months' observation period was over. The incubation period in each case was in the region of 50 days—a little longer than the average—but the primary lesions were of normal aspect and *Spirochaeta pallida* was easily found. In the case of patients with genital sores of any kind, coincidental gonorrhoea is best treated with sulphonamides.

So common is a primary fever in the penicillin treatment of early syphilis that, in the early days, I had the temperatures recorded four-hourly in patients treated for gonorrhoea, intending to observe especially closely any in whom fever

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developed. None ever did show a rise in temperature, and I have abandoned this idea as a method of demonstrating an undeveloped syphilitic infection.

Summary and conclusions

(1) Penicillin is the most potent remedy now at our disposal for the treatment of gonorrhoea.

(2) With a dosage of 100,000 units and upwards, given in 4 or 5 separate injections over 8–12 hours, a rapid clinical cure of at least 90 per cent of cases of uncomplicated acute or sulphonamide-resistant gonorrhoea can be confidently expected. Of the failures which show a reappearance of gonococci in secretions, a large percentage can be cured by further treatment with penicillin.

(3) Adjuvant treatment is sometimes required for residual urethritis due to secondary infection.

(4) Complicated cases with closed foci of infection do not always react well to penicillin. In such cases foci of infection must be drained before treatment with penicillin is begun.

(5) The best method of treatment of gonorrhoea with penicillin, in the present state of our knowledge, is with doses of not less than 100,000 units given intramuscularly in 4 or 5 separate injections at two-hourly or three-hourly intervals over a period of 8–12 hours. Patients with a gonococcal relapse after penicillin treatment should be re-treated with a higher dosage than that originally used and, if this is unsuccessful, two "courses" of penicillin at 24 hours' interval should be tried.

Part of the above material has appeared in French in *La Presse Médicale* for 8th October, 1945.

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DISCUSSION ON THE PRECEDING PAPERS

Brig. T. E. Osmond (the President) thanked Col. Harrison for reading Col. Pillsbury's paper. He said that he had hoped to collect observations on a considerable number of cases; a large number had been treated, but the patients moved about so quickly that one man's cases today were another man's tomorrow. He had succeeded in getting 148 cases of which 143 were perfectly satisfactory at the end of 6 months, with the possible exception of 4 patients who had refused cerebrospinal fluid examination. There were 3 serological relapses and 2 probable reinfections. If the latter were counted as relapses, the figures would make 3 per cent of relapses, but it had to be remembered that in a certain number of cases relapse had occurred after penicillin therapy before 6 months had passed, so that the actual relapse rate was considerably above 3 per cent.

In one theatre of war, out of 1,471 cases there were 18 infectious relapses or reinfections: 1·2 per cent. The old difficulty of distinction between relapse and reinfection would crop up, and he felt that all recrudescences should be regarded as relapses unless it was certain that they were reinfections. Reinfections would occur if penicillin were the curative agent that it was